
محاضره سلاحف النينجا
دكتور مايكل انجلو

easy

Opioids are often used in acute care :

- After the trauma resulting in **spinal cord injury (**SCI), **strong opioids (**such as **morphine)** are possibly used, and would have been very good at controlling the acute pain of the injury.

- **Over time however**, this situation changes and opioids become less and less effective. **For chronic pain, opioids are NOT very effective at all**, and they often have very **severe and unpleasant side effects**

Mechanism of action:

Opioid drugs produce their action by acting on opioid receptors:

- **Opioid receptors are membrane receptors coupled to G-protein:**

  1- ⇩ Adenylate cyclase → ⇩ cAMP.

  2- Open K^+-Channel → Hyperpolarization.

  3- Block Ca^{2+}-Channel

- **Types of opiod receptors and action results of their activation:**

  1- **Mu (μ_1 & μ_2):** Analgesia (Spinal & Supra-spinal), Euphoria, Sedation, Dependence, ↓ R.C., Miosis & Constipation.

  2- **Kappa (κ_1, κ_2 & κ_3):** Analgesia (Spinal & Supra-spinal), Dysphoria, Psychotomimetic, Less ↓ R.C. & Less Miosis

  3- **Delta (δ_1 & δ_2):** Analgesia (Spinal mainly) & Constipation.

It is to be noted that :

- There are a range of medications that can be helpful for spinal cord injury pain after the acute phase :
- It is very important to match the type of medication to the type of pain for the best results:

➢ Musculoskeletal pain:

responds well to simple analgesics (paracetamol, NSAIDs)

➢ Neuropathic pain :

Some of the anti-convulsants (or anti-epileptics) are used like gabapentin and pre-gabalin and they work by reducing the excitability and the abnormal firing in damaged nerves after spinal cord injury.

Contraindications of Morphine:

- ***1- Head injury:***
  - ***a- Miosis → Interfere with proper diagnosis.***
  - ***b- Morphine ⇩ R.C. → ⇧ CO_2 → Cerebral V.D. → ⇧ Synthesis of C.S.F. → ⇧ Intra-cranial tension → More ⇩ R.C.***
- 2- ⇧ Intra-cranial tension.
- 3- Epilepsy.
- 4- Respiratory diseases e.g. Asthma & C.O.P.D.
- 5- Acute abdomen → Morphine → Analgesia → Interfere with proper diagnosis.
- ***6- Pregnancy & Labor:***
  - ***a- Pregnancy → Addict fetus → Withdrawal symptoms after labor.***
  - ***b- Labor → Neonatal asphyxia***.
- 7- Liver disease → Deficient metabolism.
- 8- Extremities of age → Deficient metabolism.

Advantages of combination of carbidopa with levodopa:

1. Lowers the daily dose of levodopa by four- to fivefold
2. Decreases the severity of the peripheral side effects
3. Increases the central effect

I) Dopaminergic drugs

Most effective

1) Levo dopa/ Carbidopa

Main stay of therapy

Mechanism of action:

Levo dopa

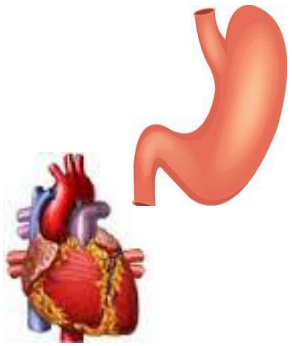
- An immediate **precursor of DA** which **crosses BBB** (DA can not) → converted **centrally** via **Dopa Decarboxylase (DD)** enzyme into **DA**.

Carbidopa

- Without *carbidopa*, much of levodopa is decarboxylated to DA in the periphery, resulting in peripheral adverse effects.
- **Carbidopa**, a **peripheral Dopa Decarboxylase enzyme** inhibitor → ↓ levodopa metabolism peripherally → ↑ its availability centrally.

Adverse effects of levodopa:

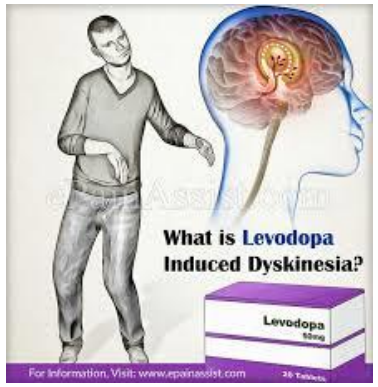
A) Peripheral (↓ with carbidopa)



- GIT: Anorexia, nausea, and vomiting (CTZ stimulation), ↑ HCl
- CVS: postural hypotension and arrhythmias (C.I in ISHD)

B) Central (↑ with carbidopa)

- Confusion, Hallucinations, psychosis (especially in the elderly)
- Abnormal involuntary movements (dyskinesias) (↑DA in basal ganglia)



C) Fluctuations in response

- End of dose akinesia
- On-off effect

Fentanyl (Synthetic)

- 1- Derivative of *Meperidine*.
- 2- **Strong** μ-Agonist → **Strong** Analgesic → **80** Times > Morphine
- 3- *High Lipid solubility*: I.V. → Rapid Onset + Short duration (Redistribution)
- 4- Used as *I.V. Anesthesia*:
  - a- Fentanyl alone, *But* → Vomiting.
  - b- Fentanyl + Droperidol (Major tranquillizer) → *Neurolept- Analgesia*
  - c- Fentanyl + Droperidol + Nitrous oxide → *Neurolept-Anesthesia*
  - *NB) The emetic effect of Fentanyl is # Anti-emetic effect of Droperidol.*
- 5- *Adverse Effects* → Vomiting, Marked ⇩ RC & ⇧ Muscle tone → Trunkal rigidity

N.B.: Droperidol is a dopamine antagonist: blocks dopamine receptors in the CTZ, TTT of nausea & vomiting

mcq

Acute Morphine Poisoning:

- a- *Manifestations*: Coma + PPP + Hypoventilation, Hypoxia, Hypotension & Hypothermia.
- b- *Cause Of Death* $\rightarrow$ Respiratory Failure.
- c- *Treatment*:
  - Artificial respiration. No pure O_2 $\rightarrow$ Apnea.
  - Stomach wash in *Every* case even after parenteral poisoning.

    Use K-Permanganate + Charcoal + $MgSO_4$.
  - Specific Morphine Antagonists e.g. ***Naloxone*** (0.4 mg I.V.).

Dantrolene cont.

Dantrolene uses:

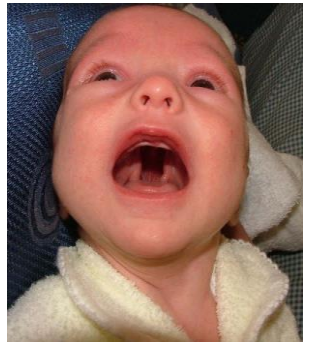
Dantrolene has demonstrated efficacy for spasticity in:

- Spinal cord injury, cerebral palsy, and multiple sclerosis.
- Brain injury.
- The drug of choice for the prevention and ***treatment of malignant hyperthermia***, (a life-threatening genetic disorder triggered by volatile anesthetics and the depolarizing neuromuscular blocking agent succinylcholine)

Phenytoin side effects (8H)

P alate H e N +2M

- **Dose related side effects:** Nystagmus, diplopia, ataxia, sedation and drowsiness
- **Non dose related:**
  - Gingival Hyperplasia (gum hypertrophy), Hirsutism, acne, rash, Hepatotoxicity and coarsening of features
- **Chronic use:** decrease bone mineral denisty (vit D metabolism leading to Hypocalcemia), megaloblastic anemia, Hyperglycemia, Neuropathy
- Hypersensitivity: rash, IV infusion side effects: phlebitis and hypotension
- Pregnancy category D

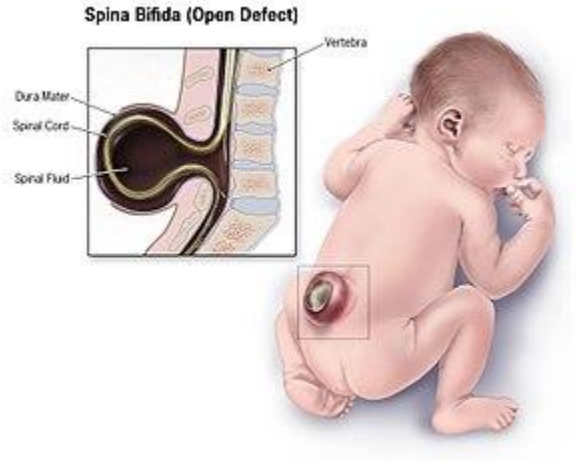


fetal hydantoin syndrome

- Cleft lip and palate
- Congenital Heart disease
- Hypoplasia
- Slowing of growth
- Mental deficiency

Valproate side effects

- Most common nausea, vomiting and mild drowsiness
- Fatal Hepatotoxicity
- Fatal pancreatitis
- Hematological: Thrombocytopena
- Suicidal thoughts
- Severe birth defect (spina bifida, and lower IQ)



Ethosuxamide

- block t type ca channel
- Uses in ***absence seizures***
- Side effects:
  - gastric distress, nausea and vomiting
  - Pregnancy category C
  - It ***may increase frequency of grand mal seizures*** in some patients

Adverse effects

1) MAOIs + tyramine:

- Individuals receiving a MAOI are **unable to degrade tyramine obtained from the diet**.
- **Tyramine** causes the release of large amounts of stored catecholamines from nerve terminals, resulting in **a hypertensive crisis**
- Patients **must avoid** tyramine-containing foods.
  - **Tyramine** is contained **in foods**, such as **aged cheeses** and **meats**, **chicken liver**, **smoked fish**, and **red wines**.
- **Management of tyramine-induced hypertension**

  By: Phentolamine or prazosin

SSRIs - Pharmacokinetics

- **Fluoxetine:**

  - has a much longer half-life (50 hours)

    sustained release preparation (once-weekly)

  - its metabolite S- norfluoxetine is as potent as the parent compound & its half-life is ~ 10 days.

- **Fluoxetine and Paroxetine**

  Potent inhibitors of a hepatic cytochrome P450 isoenzyme (CYP2D6) responsible for the elimination of Tricyclic antidepressant drugs, neuroleptic drugs, and some antiarrhythmic and β-antagonist drugs.

Chlorpromazine

- Explain the adverse effects of chlorpromazine
- **Side Effects**

1- C.N.S.:

- Drowsiness & *Sedation(antihistaminic effects)*
- Extrapyramidal Manifestations:

1- Dystonia (painful muscle spasm→ twisting).

2- Akathisia (motor restlessness).

3- Parkinsonism(shuffling gait, masked face, M. rigidity)

4- Tardive dyskinesia(involuntary movement of orofascial Muscles)

- Neurolept-malignant Syndrome:

Idiosyncratic reaction (similar to malignant hyperthermia)

Muscle rigidity, fever, altered mental status

Treated by I.V dantrolene

Chlorpromazine

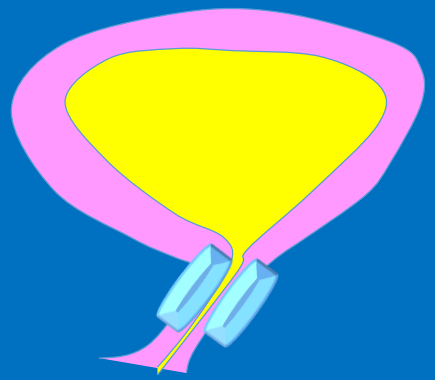
Side Effects

2. Atropine like Side Effects:

• Dry mouth

• Blurred vision & ⬆ I.O.P

• Tachycardia



• Urine retention

B) Caffeine

1- With *E*rgotamine

Cafergot in acute attack of Migraine headache.

With Aspirin or paracetamol in simple headache.

2- Poisoning by C.N.S. depressants e.g. *H*ypnotics.

NaturesPharm

B) Caffiene:

Wide safety margin

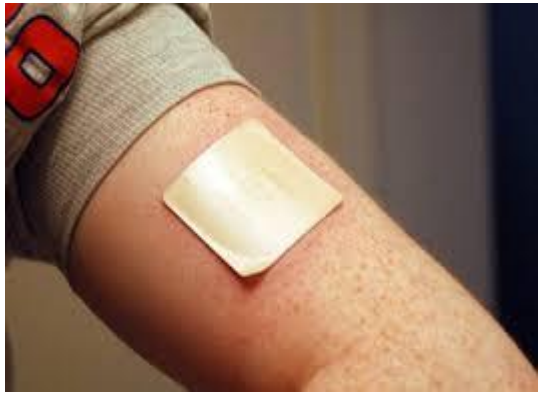
C.N.S insomnia, anxiety, and agitation, finally convulsions.

G.I.T. Hyperacidity and then emesis.

The **lethal dose** is 10 g of *caffeine* , which induces **cardiac arrhythmias.**

Death from *caffeine* is, therefore, **highly uncommon.**

Methylphenidate is available in extended-release oral formulations and as a transdermal patch for once-daily application.



pH and Local Anesthetic Activity

weak basic amine (Pka =7.9-9)

Two forms exist simultaneously

- non ionized form (cross membrane)
- ionized form (active form)

The relation between the two forms depends on

- PKa of the local anesthesia
- PH of the tissue

Extracellular & intracellular pH effect of Local anesthetic activity

- ***Extracellular pH:***
  - ↓pH (acidosis) ……more ioniz…… n
  - ↑pH (alkalosis)……more non-ionized form……..more penetration (rapid onset)
- Intracellular pH:
  - ↓pH (acidosis) …… more ionized form …….more active

•Repeated injection
•infection

•Add NaHCO3

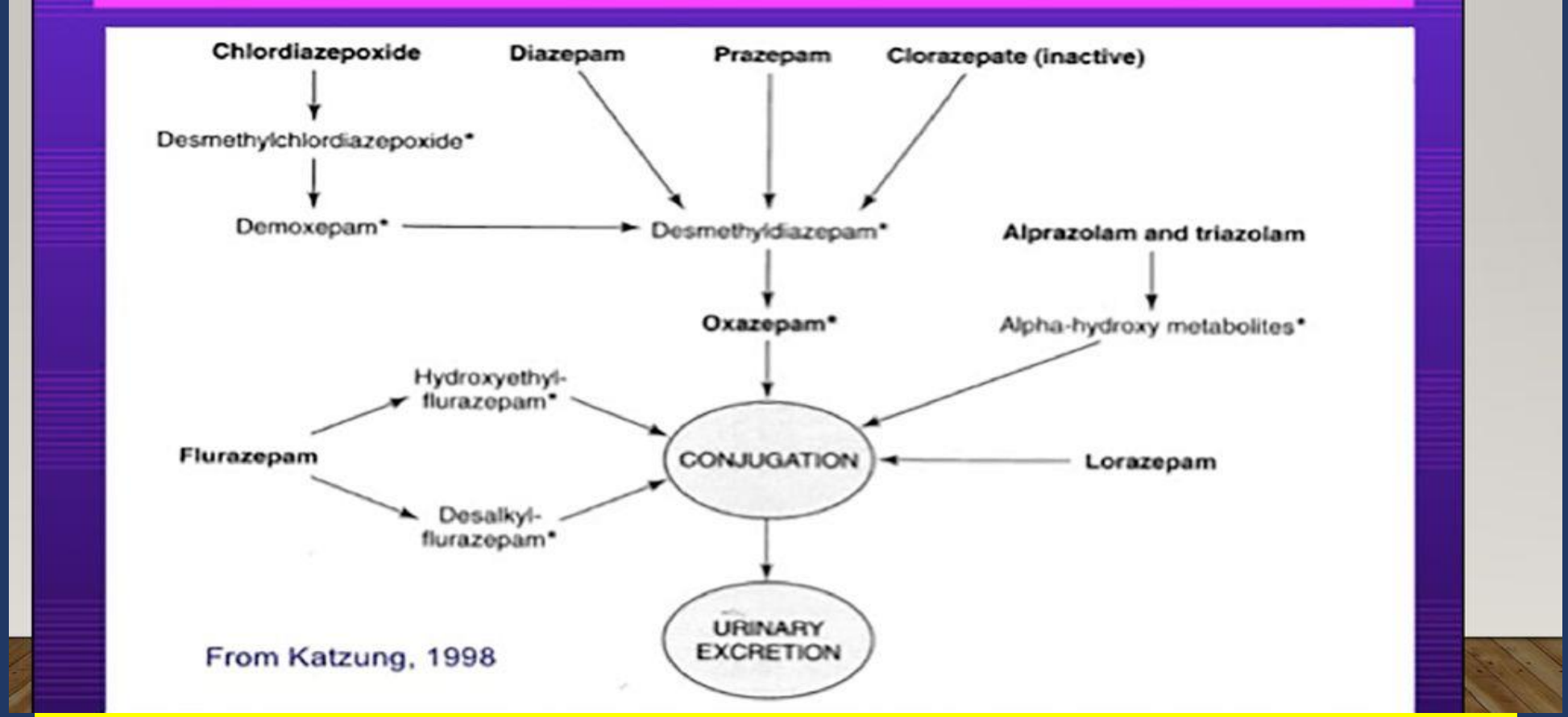
•Prepare carbonated solution

Influence of the adjuvant used

Vasoconstrictors are added to LA (except cocaine) to prolong duration of action and decrease systematic toxicity.

NB: LA except cocaine induce VD……↑absorption….. ↑systemic toxicity&↓effect

- **Epinephrine is the commonly used one**
- **In contraindication of epinephrine, Felypressin (vasopressin analogue) is used.**
- **Vasoconstrictors are CI in anesthesia of fingers, toes & nose gangrene.**



LOT = *Lorazepam*, Oxazepam, temazepam used in *liver and renal dysfunction*.

-They have no active metabolites and no CYP metabolism only conjugation (conjugation is lately affected in severe liver cirrhosis.)

-Also better in renal dysfunction as they don't heve active metabolites which is urinary excreted

Advantages of Benzodiazepines over barbiturates

1- Wide safety margin

2- Has an antidot

3- No enzyme induction

4- No porphyria

5- Less tolerance and dependence (but more

6- Less respiratory and CVS

Z- hypnotics (night calm)

Non BZD acting on BZ 1 receptors

Antagonized by flumazenil

Sedative hypnotics that are used in non anxiety induced insomnia

BZDs toxicity:

1- Prolonged sleep and coma

Same symptomatic treatment AS barbiturates

2- Flumazenil an antidot

Mechanism of action:

- *Aspirin* is a weak organic acid that **irreversibly acetylates** (and, thus, inactivates) **cyclooxygenase**
- The **other NSAIDs**, are all **reversible** inhibitors of cyclooxygenase.
- Aspirin (acetylsalicylic acid) blocks the cyclooxygenase pathway by **inhibiting COX1 and COX2 (non selective)**
- This results in ↓ **PGs, prostacyclin and thromboxane**.

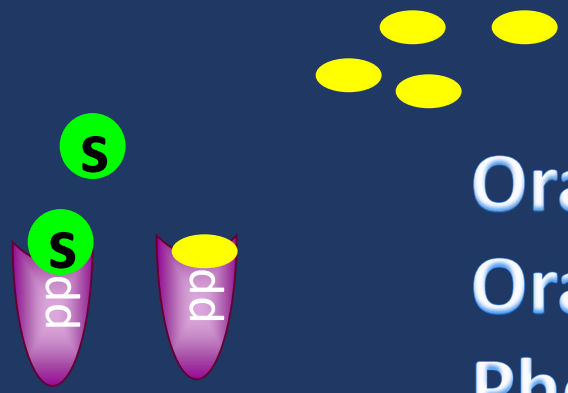
b. Antipyretic action:

- Salicylates **lower body temperature** in patients with fever **by inhibiting PGE2 synthesis and release.**
- *Aspirin and other NSAIDs* ***reset*** **the "thermostat" in CNS** toward normal. This rapidly **lowers the body temperature** of febrile patients by increasing heat loss as a result of **peripheral vasodilation and sweating.**
- *Aspirin has* ***NO*** **EFFECT on NORMAL body temperature.**

Salicylates

Drug Interactions:

- **Salicylates** displaces other drugs from plasma proteins e.g:



Oral anticoagulants
Oral hypoglycemics
Phenytoin & valporic acid

Side Effects

1- Gastric irritation:

Peptic ulcer

Bleeding

2- Bleeding Tendency (↓ platelet aggregation)

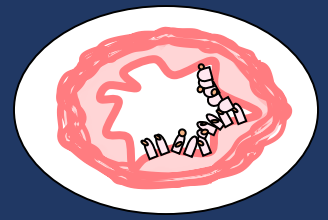
Asprin + warfarin

Small dose

3- Nephropathy

4- Aspirin-induced asthma :

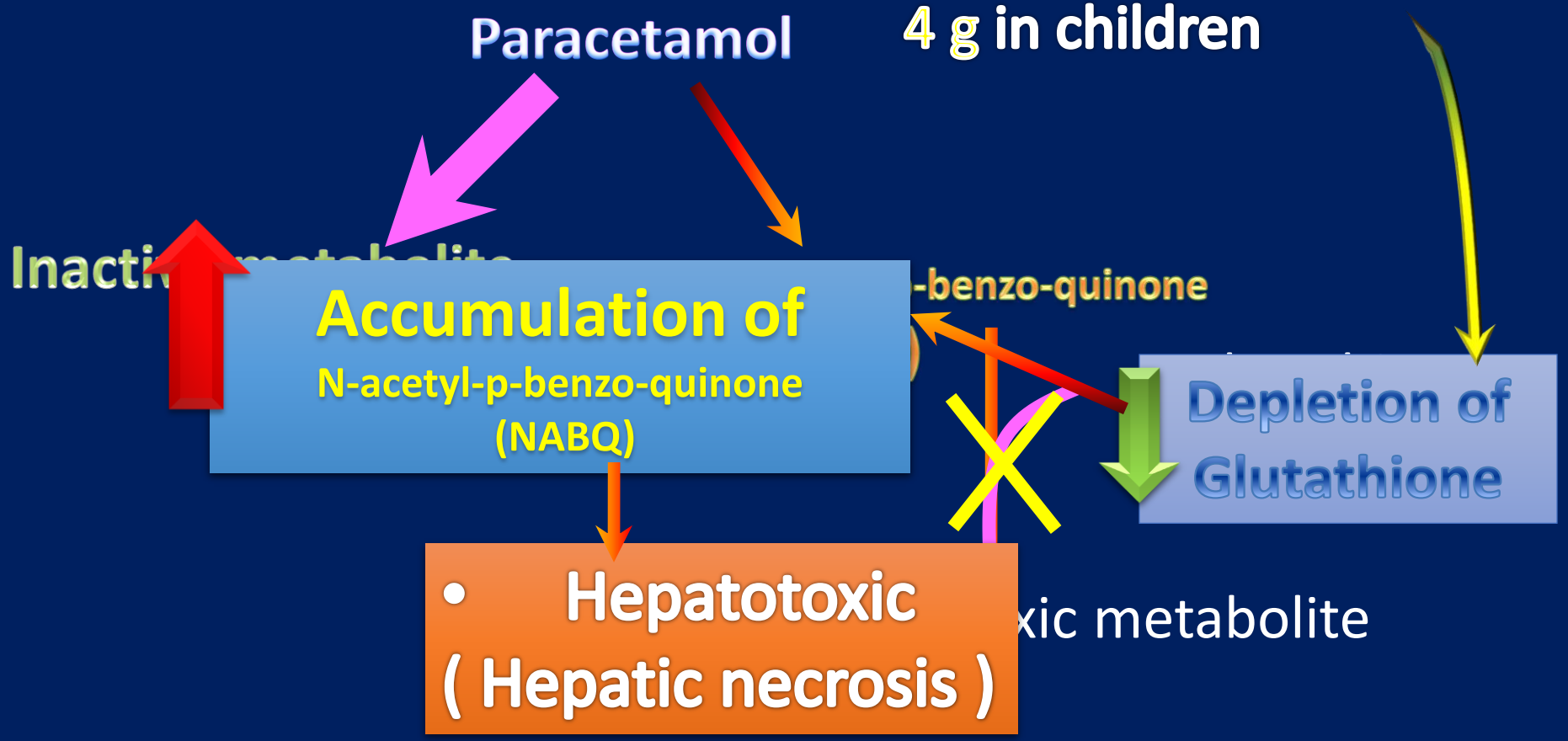
Bronchial asthma in predisposed patients



Acetaminophen

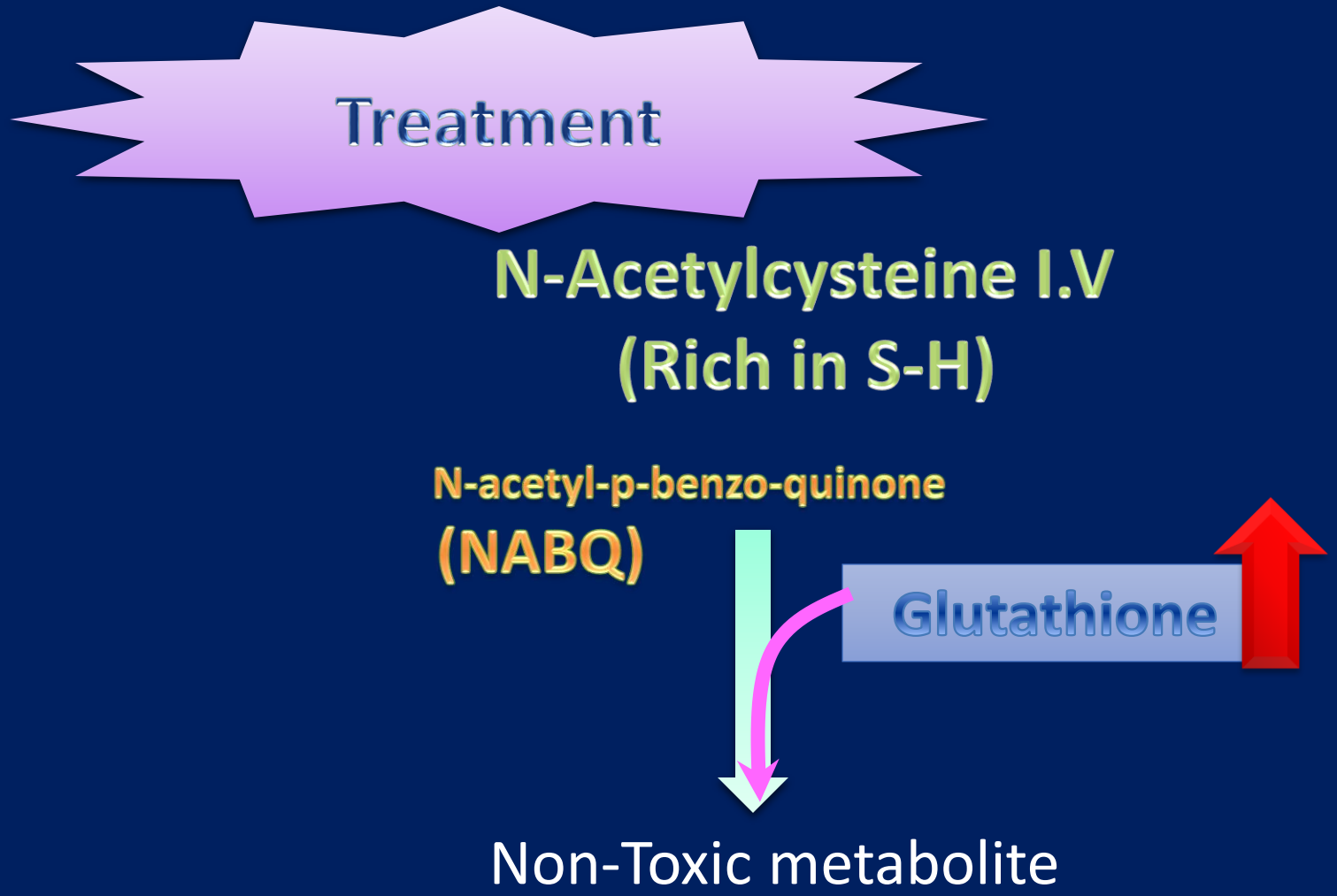
➢Acute Toxicity:

Toxic dose = single dose of 10-15 g in adults
(200mg/kg)
4 g in children



Acetaminophen

➢Acute Toxicity:



Drug therapy of migraine

Severe migraine < acute attack > when

These patients suffer 2- 3 or more attacks per month of severe throbbing headache lasting 12-4 8 hours, often accompanied by vertigo, vomiting and other symptoms; the subject is grossly incapacitated during the attack.

Treatment guide

- **Specific antimigraine**
- **antiemetics.**
- **Combination of a longer acting analgesic like naproxen with a triptan may be more suitable for patients who have prolonged migraine attacks and suffer recurrences when treated with *treiptan alone***
- **Prophylactic regimens lasting 6 months or more are recommended.**